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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/737,633	11/15/96	SAMARITANI	F P/42-60

HM22/1205
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EXAMINER	
LANDSMAN, R	
ART UNIT	**PAPER NUMBER**
1647	28

DATE MAILED: 12/05/00

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 28

Application Number: 08/737,633
Filing Date: November 15, 1996
Appellant(s): SAMARITANI ET AL.

Date mailed
12/5/02

Charles C. Achkar
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 9/11/00.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Rejected claims 1, 3, 5-7, 9 and 10 stand or fall together.

(8) Claims Appealed

A substantially correct copy of appealed claim 3 appears on page 1 of the Appendix to the appellant's brief. The minor errors are as follows: the word "claims" should be "claim."

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

5,643,566	Hanisch et al.	7-1997
4,647,454	Cymbalsita et al.	3-1987
5,004,605	Hershenson et al.	4-1991

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

A. Claims 1, 3, 7, 9 and 10 are rejected under 35 USC 103(a) as being unpatentable over Hanisch et al. (Patent No. 5,643,566).

The claims recite a liquid pharmaceutical formulation consisting of about 0.6 to 24 MIU/ml of interferon-beta, mannitol, a buffer at a pH between 3.0 and 4.0 and, optionally, albumin. Furthermore, the interferon-beta can be recombinant and the albumin can be human albumin. The present invention also recites a process for the preparation of said pharmaceutical formulation and a hermetically sealed container comprising the said formulation.

Hanisch describes formulations for the stable storage of "lipophilic proteins," including the particularly exemplified IL-2 and INF-beta (Abstract). It teaches that a formulation having essentially only INF-beta, human serum albumin and a buffer (as is obtained following practice of the prescribed purification protocol) may be prepared at an acidic pH, preferably 3.5, and that under such conditions "[t]he beta-INF formulation will remain stable and soluble." (Column 12, lines 53-65). It further teaches that the formulation "can be maintained as a liquid with or without a carbohydrate stabilizer," and that, following the optional addition of such stabilizer, the formulation may be lyophilized. Id. The patent teaches that a number of carbohydrate stabilizers, including mannitol, may be employed in the formulation it describes (column 9, lines 21-37). Hanisch does not exemplify a formulation consisting of INF-beta, HSA, a buffer and mannitol.

However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have prepared a liquid formulation consisting of INF-beta, HSA, a buffer at pH 3.5 and mannitol because Hanisch teaches that such a formulation will be stable and may be lyophilized, if desired, prior to reconstitution for therapeutic use. It further would have been obvious to have dispensed the formulation in unit dosage quantities into sterile containers for lyophilization because Hanisch teaches that the "lypohilized formulation can then be reconstituted for clinical administration" and one of ordinary skill in the art would have realized that such use would require sterile containment according to conventional practice in the art. Therefore, the claimed invention would have been *prima facia* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

B. Claim 5 is rejected under 35 USC 103(a) as being unpatentable over Hanisch et al. as applied to claims 1,3,7,9 and 10 above, and further in view of Cymbalista et al. (Patent No. 4,647,454) Cymbalista et al. teach that acetate buffer at a pH of 3.5 is suitable for making stable formulations of IFN-beta (column 1, lines 47-56).

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to have prepared a formulation of INF-beta as generally described by Hanisch et al. employing a pH 3.5 acetate buffer as described by Cymbalista because Cymbalista teaches that INF-beta is stable in acetate buffer at pH 3.5 and that such buffer is suitable for preparing stable pharmaceutical formulations of INF-beta. The ordinarily skilled artisan would have realized, in view of the teachings of the references considered collectively, that the acetate buffer described by Cymbalista would be especially suitable for use in the formulation described by Hanisch because of its appropriate pKa. The claimed invention would have been prima facia obvious as a whole at the time it was made, especially in absence of evidence to the contrary.

C. Claim 6 is rejected under 35 USC 103(a) as being unpatentable over Hanisch et al. as applied to claims 1,3,7,9 and 10 above, and further in view of Hershenson et al. (Patent No. 5,004,605). Hershenson et al. teach that it is desirable to employ a buffer at a pH between 2 and 4, preferably at a concentration of 10 to 25 mM, to prepare stable formulations of IFN-beta (column 9, lines 13-20).

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have prepared a formulation of INF-beta as described generally by Hanisch, employing a buffer of pH 2-4 and a concentration of 10-25 mM because Hershenson teaches INF-beta in such a buffer and that such a buffer is suitable for preparing stable pharmaceutical formulations of the IFN. The ordinarily skilled artisan would have realized, in view of the teachings of the references considered collectively, that 10-25 mM buffers described by Hershenson would be especially suitable for use in the formulation described by Hanisch. The claimed invention would have been *prima facia* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

(11) Response to Argument

With regard to rejected claims 1, 3, 7, 9 and 10, Applicants argue that this claim sets forth a liquid pharmaceutical formulation consisting of from about 0.6 to 24 MIU/ml of interferon, mannitol, a buffer at a pH between 3.0 and 4.0 and, optionally, albumin.

Applicants argue that a person of ordinary skill in the art would not have any expectation of success using mannitol, to stabilize low concentrations of interferon-beta in a liquid state at a low pH and that there is nothing in Hanisch et al., either alone or in combination with Cymbalista and Hershenson, that teaches the use of mannitol at a low pH in a stable liquid composition containing interferon-beta. This argument has been considered but is not deemed persuasive because Hanisch et al. teach (column 5, lines 6-51) that recombinant interferon-beta is stable and soluble at a pH range of approximately 2-4 and that such a low pH solution containing lipophilic proteins, such as interferon-beta, do not require a

stabilizer. Therefore, these low pH formulations can be maintained as a liquid, and used pharmaceutically.

However, Hanisch et al. do teach that a carbohydrate stabilizer, such as dextrose or mannitol can be added thereto, as claimed by the present invention and that the formulation can be optionally lyophilized later. Therefore, Hanisch et al. do teach a liquid pharmaceutical formulation consisting of recombinant interferon-beta, mannitol, and a buffer between 3.0 and 4.0. In fact, Hanisch et al. teach that carbohydrate stabilizers alone can only be used in formulations maintained at pH of 2-4 (column 9, lines 50-52). Furthermore, Applicants argue that Hanisch et al. teach that human serum albumin is preferred for high pH formulations using interferon-beta. However, this reference does not teach that a high pH is absolutely necessary when using human albumin, only that it is preferred.

Finally, Applicants argue that the compositions of Hanisch et al. contain higher concentrations of interferon-beta (50 MIU/ml) immediately prior to lyophilization, implying that these higher concentrations are necessary to achieve stability and efficiency during lyophilization. However, Hanisch et al. teach that these formulations containing recombinant interferon-beta could be maintained as a liquid.

Example 1 of Hanisch et al. describes a unit dose formulation containing IFN-beta at 0.23 mg, or 50 x 10^6 IU ('566 at column 21, lines 15-24). That is not, however, the only unit dosage known in the art. Hershenson et al. '605, for example, teaches that a solution containing 0.25 mg ml^{-1} of IFN-beta is suitable for preparing "normal dosage" formulations, whereas a "high dosage" formulation will contain on the order of 2 mg ml^{-1}, and a "low dosage" formulation, 0.125 mg ml^{-1} of IFN-beta ('605 at column 8, lines 47-60). Hanisch et al., moreover, exemplifies the preparation of a formulation having only 0.06 mg of IFN-beta ('566 at column 24, lines 34-38).

It would have been obvious to prepare a formulation of IFN-beta containing only half the amount exemplified by Hanisch et al. at Example 1, *i.e.*, on the order of about 0.125 mg or 25 x 10^6 IU per vial, because Hershenson et al. teach a range of unit dosages are employed in the art for pharmaceutical preparations of IFN-beta and that a solution of 0.125 mg ml^{-1} affords an exemplary "low dose"

formulation. It would have been obvious to do so either by using half as much solution as described in Hanisch et al. Example 1, or by preparing a solution containing IFN-beta at half the exemplified concentration. The artisan would have expected the latter approach to be suitable for lyophilization according to the method of the '566 patent because Hanisch et al. exemplify a stable lyophilized preparation containing only 0.06 mg, or *ca.* 12.5 x 10^6 IU of IFN-beta.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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November 30, 2000

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